at least at page 13, lines 7-10 and page 22, lines 11-14. Claims 26-28 and 30-32 have been withdrawn from consideration as being drawn to a non-elected invention.

The claims define methods for delivering a drug to a patient. A formulation which contains a highly porous matrix is administered to the patient. The porous matrix contains microparticles of drug and a wetting agent. The porosity of the matrix is defined in terms of its TAP density and total surface area. The TAP density is less than or equal to 1.0 g/mL and the total surface area of the dry matrix is greater than or equal to 0.2 $m^2/g$. The microparticles of drug, which are part of the matrix, have a mean diameter of 0.1 to 5 μm and a total surface area of greater than about 0.5 $m^2/mL$. Porous matrices with these characteristics have faster rates of dissolution following administration to a patient, as compared to non-porous matrix forms of the drug.

**Rejection Under 35 U.S.C. § 112, second paragraph**

Claim 29 was rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

The M.P.E.P. explains that the primary purpose of the § 112 definiteness requirement is "to ensure that the scope of the claims is clear so that the public is informed of the boundaries of what constitutes infringement of the patent" and "to provide a clear measure of what applicants regard as the invention". (M.P.E.P. § 2173)

The scope of claim 29, as amended, is clear to one of ordinary skill in the art. Claim 29 depends from claim 23 and further defines the formulation as being suspended in an aqueous

solution that is suitable for parenteral administration. Claim 23 states that the *drug* is in the form of microparticles. The drug is *one component* of the matrix; and the matrix is one component of the formulation. Therefore claim 23 encompasses the administration of a number of different types of formulations, including suspensions, and is not limited to microparticulate formulations. Claim 29 further defines the formulation by requiring it to be in a solution which can be administered parenterally. Such formulations are defined in the specification at least at page 22, lines 11-17. One of ordinary skill in the art is familiar with formulations that are suitable for parenteral administration. For example, the enclosed reference, H. Ansel *et al.*, Pharmaceutical Dosage Forms and Drug Delivery Systems, 6th Ed, pages 81-83 and 286-294 (Williams & Williams 1995), describes formulations that are applied parenterally, along with appropriate solvents and additional components. Therefore, claim 29, as amended, is definite.

**Rejection Under 35 U.S.C. § 102**

Claims 23-25, 29, and 33-35 were rejected under 35 U.S.C. § 102(e) as being anticipated by U.S. Patent No. 5,942,253 to Gombotz *et al.* ("Gombotz"). Applicants respectfully traverse this rejection.

***Applicants' Methods***

Applicants' methods are directed to administering to a patient a formulation which contains a highly porous matrix with drug microparticles. The porosity of the matrix is defined in terms of its TAP density and total surface area. The TAP density is less than or equal to 1.0 g/mL and the total surface area of the dry matrix is greater than or equal to 0.2 $m^2/g$ (see claim

23). Matrices with porosities as defined by the claims dissolve very rapidly. Thus, the claimed methods can be used to deliver compounds which are poorly water soluble quickly to a patient.

The examples and figures in the specification demonstrate how rapidly these matrices dissolve. For example, Figure 2 graphically depicts the rate of dissolution for griseofulvin, an extremely water-insoluble drug, in the porous matrices defined by the claims. Within *five minutes*, 80% of the composition dissolved, compared to only 30% of the normal bulk composition. Figure 3 depicts the rate of dissolution for compositions containing nifedipine. Greater than 90% of the porous matrices containing nifedipine dissolve within *five minutes*, compared to only 15% of the normal bulk drug. Similarly, Figure 5 demonstrates that 100% of the porous matrices containing paclitaxel dissolve within *five minutes*, compare to only about 20% of the normal bulk drug.

***Gombotz***

Gombotz is not directed to the highly porous matrices defined by the claims. Gombotz discloses microparticles for the *prolonged*, controlled release of human granulocyte macrophage colony stimulating factor (GM-CSF) (see col. 1, lines 4-7). Gombotz teaches that GM-CSF has a linear release from about *one day to about 60 days* (col. 4, lines 21-22). Gombotz does not even disclose data for the release of GM-CSF within a short time period (e.g. minutes to an hour). Thus, Gombotz *teaches away* from rapidly dissolving compositions. Further, nowhere does Gombotz disclose that a porous matrix with a large total surface area and low TAP density, such as required by the claims, should be formed.

Though Gombotz notes that pore forming agents may be incorporated in the matrices, these pore forming agents are water-soluble compounds, such as inorganic salts and sugars (see col. 9, lines 51-55). Gombotz teaches that the pore forming agents are added as particulates so that they comprise between 1 and 30% (w/w, polymer). As noted above, however, Gombotz merely uses these agents to control the rate of release so that a *prolonged* linear release of the GM-CSF occurs. Therefore, Gombotz does not teach nor suggest the formation of a porous matrix, as defined by claim 1 and its dependent claims. Therefore claims 23-25, 29, and 33-35 are novel and non-obvious in view of Gombotz.

Further, Gombotz does not teach that the drug in the matrix is in the form of microparticles, let alone describe the size of the drug particles. Gombotz only mentions that the size of the overall microspheres ranges from 1 to 1000 μm (page 8, line 25). Therefore Gombotz does not disclose microparticles of a drug with a diameter of about 0.1 to 5 μm and a total surface area greater than about 0.5 $m^2$/mL.

Allowance of claims 23-35, as amended, is respectfully solicited.

Respectfully submitted,

Rivka D. Monheit

Rivka D. Monheit
Reg. No. 48,731

Date: December 12, 2002

HOLLAND & KNIGHT LLP
One Atlantic Center, Suite 2000
1201 West Peachtree Street
Atlanta, Georgia 30309-3400
(404) 817-8514
(404) 817-8588 (Fax)

**Certificate of Facsimile Transmission**

I hereby certify that this Amendment and Response to Office Action, and any documents referred to as attached therein are being facsimile transmitted on this date, December 12, 2002 to the Commissioner for Patents, U.S. Patent and Trademark Office, Washington, DC 20231.

Pam Turnbough

Pam Turnbough

Date: December 12, 2002

U.S.S.N. 09/706,045
Filed: November 3, 2000
**MARKED UP VERSION OF AMENDED CLAIMS**

## Marked Up Version of Amended Claims Pursuant to 37 C.F.R. § 1.121(c)(1)(ii)

23. (Amended) A method of delivering a drug to a patient in need thereof, comprising administering a therapeutically or prophylactically effective amount of the drug in a formulation comprising a porous matrix which comprises a wetting agent and microparticles of the drug, wherein the microparticles have a mean diameter between about 0.1 and 5 μm and a total surface area greater than about 0.5 $m^2$/mL, and wherein the porous matrix has a TAP density less than or equal to 1.0 g/mL and/or has a total surface area of greater than or equal to 0.2 $m^2$/g and is in the form of a dry powder.

24. The method of claim 23 wherein the formulation is suitable for administration by a route selected from the group consisting of parenteral, mucosal, oral, and topical administration.

25. (Amended) The method of claim 24 wherein the parenteral route is selected from the group consisting of intravenous, intraarterial, intracardiac, intrathecal, intraosseous, intraarticular, intrasynovial, intracutaneous, subcutaneous, and intramuscular administration.

26. The method of claim 24 wherein the mucosal route is selected from the group consisting of pulmonary, buccal, sublingual, intranasal, rectal, and vaginal administration.

27. The method of claim 23 wherein the formulation is suitable for intraocular or conjunctival administration.

28. The method of claim 23 wherein the formulation is suitable for intracranial, intralesional, or intratumoral administration.

U.S.S.N. 09/706,045
Filed: November 3, 2000
**MARKED UP VERSION OF AMENDED CLAIMS**

29. (Amended) The method of claim 23 wherein the formulation is suspended in an aqueous solution suitable for parenteral administration.

30. The method of claim 23 wherein the formulation is in a tablet or capsule suitable for oral administration.

31. The method of claim 23 wherein the formulation is in a suppository suitable for vaginal or rectal administration.

32. (Amended) The method of claim 23 wherein the formulation is suitable for pulmonary administration.

33. The method of claim 23 wherein the dry powder form of the porous matrix has a TAP density less than or equal to 1.0 g/mL.

34. The method of claim 23 wherein the dry powder form of the porous matrix has a total surface area of greater than or equal to 0.2 $m^2/g$.

35. The method of claim 23 wherein the mean diameter of the microparticles is between about 0.5 and 5 μm.

# Pharmaceutical Dosage Forms and Drug Delivery Systems

*Howard C. Ansel, Ph.D.*
Panoz Professor of Pharmacy, Department of Pharmaceutics, College of Pharmacy
*The University of Georgia*

*Nicholas G. Popovich, Ph.D.*
Professor and Head, Department of Pharmacy Practice, School of Pharmacy and Pharmacal Sciences
*Purdue University*

*Loyd V. Allen, Jr., Ph.D.*
Professor and Chair, Department of Medicinal Chemistry and Pharmaceutics, College of Pharmacy
*The University of Oklahoma*

SIXTH EDITION

*A Lea & Febiger Book*

**Williams & Wilkins**
BALTIMORE • PHILADELPHIA • HONG KONG
LONDON • MUNICH • SYDNEY • TOKYO
A WAVERLY COMPANY

1995

*Executive Editor:* Donna M. Balado
Developmental Editor: Frances M. Klass
*Production Coordinator:* Peter J. Carley
*Project Editor:* Jessica Howie Martin





Accurate indications, adverse reactions, and dosage schedules for drugs are provided in this book, but it is possible they may change. The reader is urged to review the package information data of the manufacturers of the medications mentioned.

*Printed in the United States of America*

Library of Congress Cataloging in Publication Data

94 95 96 97 98
1 2 3 4 5 6 7 8 9 10

Ansel, Howard C., 1933–
Pharmaceutical dosage forms and drug delivery systems / Howard C. Ansel, Nicholas G. Popovich, Lloyd V. Allen, Jr.—6th ed.
p. cm.
Includes bibliographical references and index.
ISBN 0-683-00193-0
1. Drugs—Dosage forms. 2. Drug delivery systems.
I. Popovich, Nicholas G. II. Allen, Loyd V. III. Title.
[DNLM: 1. Dosage Forms. 2. Drug Delivery Systems. QV 785 A618i 1995]
RS200.A57 1995
615'.1—dc20
DNLM/DLC
for Library of Congress 94-22471
CIP



PRINTED IN THE UNITED STATES OF AMERICA

Print No. 4 3 2 1

the plasma on the other side of the membrane as though its pH were about 5.3.

### Rectal Route

Some drugs are administered rectally for their local effects and others for their systemic effects. Drugs given rectally may be administered as solutions, suppositories, or ointments. *Suppositories* are defined as solid bodies of various weights and shapes intended for introduction into a body orifice (usually rectal, vaginal, or urethral) where they soften, melt, or dissolve, release their medication, and exert their drug effects. These effects simply may be the promotion of laxation (as with glycerin suppositories), the soothing of inflamed tissues (as with various commercial suppositories used to relieve the discomfort of hemorrhoids), or the promotion of systemic effects (as antinausea or antimotion sickness). The composition of the suppository base, or carrier of the medication, can greatly influence the degree and rate of drug release and should be selected on an individual basis for each drug. The use of rectal ointments is generally limited to the treatment of local conditions. Rectal solutions are usually employed as enemas or cleansing solutions.

The rectum and the colon are capable of absorbing many soluble drugs. Rectal administration for systemic action may be preferred for those drugs destroyed or inactivated by the environments of the stomach and intestines. The administration of drugs by the rectal route may also be indicated when the oral route is precluded because of vomiting or when the patient is unconscious or incapable of swallowing drugs safely without choking. It is estimated that about 50% of a dose of drug absorbed from rectal administration is likely to bypass the liver, an important factor when considering those orally administered drugs that are rapidly destroyed in the liver by the first-pass effect. On the negative side, compared with oral administration, rectal administration of drugs is inconvenient, and the absorption of drugs from the rectum is frequently irregular and difficult to predict.

### Parenteral Route

The term *parenteral* is derived from the Greek words *para*, meaning beside, and *enteron*, meaning intestine, which together indicate something done outside of the intestine and not by way of the alimentary tract. A drug administered parenterally is one injected through the hollow of a fine needle into the body at various sites and to various depths. The three primary routes of parenteral administration are subcutaneous, intramuscular (I.M.), and intravenous (I.V.) although there are others such as intracardiac and intraspinal.

Drugs destroyed or inactivated in the gastrointestinal tract or too poorly absorbed to provide satisfactory response may be parenterally administered. The parenteral route is also preferred when rapid absorption is essential, as in emergency situations. Absorption by the parenteral route is not only faster than after oral administration, but the blood levels of drug that result are far more predictable, because little is lost after subcutaneous or intramuscular injection, and virtually none by intravenous injection; this also generally permits the administration of smaller doses. The parenteral route of administration is especially useful in treating patients who are uncooperative, unconscious, or otherwise unable to accept oral medication.

One disadvantage of parenteral administration is that once the drug is injected, there is no retreat. That is, once the substance is within the tissues or is placed directly into the blood stream, removal of the drug warranted by an untoward or toxic effect or an inadvertent overdose is most difficult. By other means of administration, there is more time between drug administration and drug absorption, which becomes a safety factor by allowing for the extraction of unabsorbed drug (as by the induction of vomiting after an orally administered drug). Also, because of the strict sterility requirements for all injections, they are generally more expensive than other dosage forms and require competent trained personnel for their proper administration.

DOSAGE FORMS APPLICABLE. Pharmaceutically, injectable preparations are usually either sterile suspensions or solutions of a drug substance in water or in a suitable vegetable oil. In general, drugs in solution act more rapidly than drugs in suspension, with an aqueous vehicle providing faster action in each instance than an oleaginous vehicle. As in other instances of drug absorption, a drug must be in solution to be absorbed, and a suspended drug must first submit to the dissolution process. Also, because body fluids are aqueous, they are more receptive to drugs in an aqueous vehicle than those in an oily one. For these reasons, the rate of drug absorption can be varied in parenteral products by selective combinations of drug state and supporting vehicle. For instance, a suspension of a drug in a vegetable

oil likely would be much more slowly absorbed than an aqueous solution of the same drug. Slow absorption generally means prolonged drug action, and when this is achieved through pharmaceutical means, the resulting preparation is referred to as a *depot* or *repository* injection, because it represents a storage reservoir of the drug substance within the body from which it is slowly removed into the systemic circulation. In this regard, even more sustained drug action may be achieved through the use of subcutaneous implantation of compressed tablets, termed pellets which are only slowly dissolved from their site of implantation, releasing their medication at a rather constant rate over a period of several weeks to many months. The repository type of injection is mainly limited to the subcutaneous or intramscular route. It is obvious that drugs injected intraveously do not encounter absorption barriers and thus produce only rapid drug effects. Preparations for intravenous injection must not interfere with the blood components or with circulation and therefore, with few exceptions, are aqueous solutions.

SUBCUTANEOUS INJECTIONS. The subcutaneous (hypodermic) administration of drugs involves their injection through the layers of skin into the loose subcutaneous tissue. Generally, subcutaneous injections are prepared as aqueous solutions or as suspensions and are administered in relatively small volumes of 2 mL or less. Insulin is an example of a drug administered by the subcutaneous route. Subcutaneous injections are generally given in the forearm, upper arm, thigh, or nates. If the patient is to receive frequent injections, it is best to alterate injection sites to reduce tissue irritation. After injection, the drug comes into the immediate vicinity of blood capillaries and permates them by diffusion or filtration. The capillary wall is an example of a membrane that behaves as a lipid pore barrier, with lipid-soluble substances penetrating the membrane at rates varying with their oil/water partition coefficients. Lipid-insoluble (generally more water-soluble) drugs penetrate the capillary membrane at rates which appear to be inversely related to their molecular size, with smaller molecules penetrating much more rapidly than larger ones. All substances, whether lipid-soluble or not, cross the capillary membrane at rates that are much more rapid than the rates of their transfer across other body membranes. The blood supply to the site of injection is an important factor in considering the rate of drug absorption, consequently the more proximal capillaries are to the site of injection, the more prompt will be the drug's entrance into the circulation. Also, the more capillaries, the more surface area for absorption, and the faster the rate of absorption. Some substances have the capability of modifying the rate of drug absorption from a subcutaneous site of injection. The addition of a vasoconstrictor to the injection formulation (or its prior injection) will generally diminish the rate of drug absorption by causing constriction of the blood vessels in the area of injection and thereby reducing blood flow and the capacity for absorption. This principle is utilized in the administration of local anesthetics by employing the vasoconstrictor epinephrine. Conversely, vasodilators may be employed to enhance subcutaneous absorption by increasing blood flow to the area. Physical exercise can also influence the absorption of drug from an injection site. Diabetic patients who rotate subcutaneous injection sites and then do physical exercise, e.g., jogging, must realize the onset of insulin activity might be influenced by the selected site of administration. Because of the movement of the leg and blood circulation to it during running, the absorption of insulin from a thigh injection site would be expected to be faster than that from an abdominal injection site.

INTRAMUSCULAR INJECTIONS. Intramuscular injections are performed deep into the skeletal muscles, generally the gluteal or lumbar muscles. The site is selected where the danger of hitting a nerve or blood vessel is minimal. Aqueous or oleaginous solutions or suspensions may be used intramuscularly. Certain drugs, because of their inherent low solubilities, provide sustained drug action after an intramuscular injection. For instance, one deep intramuscular injection of a suspension of penicillin G benzathine results in effective blood levels of the drug for seven to ten days.

Drugs which are irritating to subcutaneous tissue are often administered intramuscularly. Also, greater volumes (2 to 5 mL) may be administered intramuscularly than subcutaneously. When a volume greater than 5 mL is to be injected, it is frequently administered in divided doses using two injection sites. Injection sites best are rotated when a patient is receiving repeated injections over a period of time.

INTRAVENOUS INJECTIONS. In the intravenous administration of drugs, an aqueous solution is injected directly into the vein at a rate commensurate with efficiency, safety, comfort to the pa-

tient, and the desired duration of drug response. Drugs may be administered intravenously as a single, small-volume injection or as a large-volume, slow intravenous drip infusion (as is common following surgery). Intravenous injection allows the desired blood level of drug to be achieved in an optimal and quantitative manner. Intravenous injections are usually made into the veins of the forearm and are especially useful in emergency situations where immediate drug response is desired. It is essential that the drug be maintained in solution after injection and not be precipitated within the circulatory system, an event that might produce emboli. Because of a fear of the development of pulmonary embolism, oleaginous bases are not usually intravenously administered. However, an intravenous fat emulsion is used therapeutically as a caloric source for patients receiving parenteral nutrition whose caloric requirements cannot be met by glucose. It may be administered either through a peripheral vein or a central venous catheter at a distinct rate to help prevent the occurrence of untoward reactions.

INTRADERMAL INJECTIONS. These injections are administered into the corium of the skin, usually in volumes of about a tenth of a milliliter. Common sites for the injection are the arm and the back. The injections are frequently performed as diagnostic measures, as in tuberculin and allergy testing.

### Epicutaneous Route

Drugs are administered topically, or applied to the skin, for their action at the site of application or for systemic drug effects.

In general, drug absorption via the skin is enhanced if the drug substance is in solution, if it has a favorable lipid/water partition coefficient, and if it is a nonelectrolyte. Drugs that are absorbed enter the skin by way of the pores, sweat glands, hair follicles, sebaceous glands, and other anatomic structures of the skin's surface. Because blood capillaries are present just below the epidermal cells, a drug that penetrates the skin and is able to traverse the capillary wall finds ready access to the general circulation.

Among the few drugs currently employed topically to the skin surface for percutaneous absorption and systemic action are nitroglycerin (antianginal), nicotine (smoking cessation), estradiol (estrogenic hormone), clonidine (antihypertensive), and scopolamine (antinausea/antimotion sickness). Each of these drugs is available for use in the form of transdermal delivery systems fabricated as an adhesive disc or patch which slowly releases the medication for percutaneous absorption. Additionally, nitroglycerin is available in an ointment form of application to the skin's surface for systemic absorption. Nitroglycerin is employed therapeutically for ischemic heart disease, with the transdermal dosage forms becoming increasingly popular because of the benefit in patient compliance through their long-acting (24 hours) characteristics. The nitroglycerin patch is generally applied to the arm or chest, preferably in a hair-free or shaven area. The transdermal scopolamine sytem is also in the form of a patch to be applied to the skin; in this case, behind the ear. The drug system is indicated for the prevention of nausea and vomiting associated with motion sickness. The commercially available product is applied to the postauricular area several hours before need (as prior to an air or sea trip) where it releases its medication over a period of 3 days. The concepts of transdermal therapeutic systems are discussed further in Chapter 10.

For the most part, pharmaceutical preparations applied to the skin are intended to serve some local action and as such are formulated to provide prolonged local contact with minimal absorption. Drugs applied to the skin for their local action include antiseptics, antifungal agents, anti-inflammatory agents, local anesthetic agents, skin emollients, and protectants, against environmental conditions, as the effects of the sun, wind, pests, and chemical irritants. For these purposes drugs are most commonly administered in the form of ointments and related semisolid preparations such as creams and pastes, as solid dry powders, aerosol sprays or as liquid preparations such as solutions and lotions.

Pharmaceutically, ointments, creams, and pastes are semisolid preparations in which the drug is contained in a suitable base (ointment base) which is itself semisolid and either hydrophilic or hydrophobic in character. These bases play an important role in the proper formulation of semisolid preparations, and there is no single base universally suitable as a carrier of all drug substances or for all therapeutic indications. The proper base for a drug must be determined individually to provide the desired drug release rate, staying qualities after application, and texture. Briefly, *ointments* are simple mixtures of drug substances in an ointment base, whereas *creams* are semisolid emulsions and are generally less

# 8 Parenteral Medications and Sterile Fluids

CONSIDERED IN this chapter are important pharmaceutical dosage forms that have the common characteristic of being prepared to be sterile; that is, free from contaminating microorganisms. Among these sterile dosage forms are the various small- and large-volume injectable preparations, irrigation fluids intended to bathe body wounds or surgical openings, dialysis solutions, biological preparations as vaccines, toxoids, antitoxins, and blood replenishment products. Sterility in these preparations is of utmost importance because they are placed in direct contact with the internal body fluids or tissues where infection can easily arise. Ophthalmic preparations which are also prepared to be sterile will be discussed separately in Chapter 11.

## Injections

Injections are sterile, pyrogen-free preparations intended to be administered parenterally. The term *parenteral* refers to the injectable routes of administration. The term has its derivation from the Greek words *para* and *enteron*, meaning outside of the intestine, and denotes routes of administration other than the oral route. *Pyrogens* are fever-producing organic substances arising from microbial contamination and are responsible for many of the febrile reactions which occur in patients following intravenous injection. Pyrogens and the determination of their presence in parenteral preparations will be discussed later in this chapter. In general, the parenteral routes of administration are undertaken when rapid drug action is desired, as in emergency situations, when the patient is uncooperative, unconscious, or unable to accept or tolerate medication by the oral route, or when the drug itself is ineffective by other routes. With the exception of insulin injections, which are commonly *self*-administered by diabetic patients, most injections are administered by the physician, his assistant, or nurse in the course of medical treatment. Thus injections are employed mostly in the hospital, extended care facility, and clinic and less frequently in the home. An exception would be in *home health care* programs in which health professionals pay scheduled visits to patients in their homes, providing needed treatment, including intravenous medications. These programs enable patients who do not require or are unable to pay for more expensive hospitalization to remain in the familiar surroundings of their homes while receiving appropriate medical care. The pharmacist supplies injectable preparations to the physician and nurse, as required for their use in the institutional setting, clinic, office, or home health care program.

Perhaps the earliest injectable drug to receive official recognition was the hypodermic morphine solution which appeared first in the 1874 addendum to the 1867 British Pharmacopeia, and later, in 1888 in the first edition of the National Formulary of the United States. Today, there are literally hundreds of drugs and drug products available for parenteral administration.

Interesting historical accounts of the origin and development of injection therapy may be found in the references cited.

### *Parenteral Routes of Administration*

Drugs may be injected into almost any organ or area of the body, including the joints *(intra-articular)*, a joint-fluid area *(intrasynovial)*, the spinal column *(intraspinal)*, into spinal fluid *(intrathecal)*, arteries *(intra-arterial)*, and in an emergency, even into the heart *(intracardiac)*. However, most commonly injections are performed into a vein *(intravenous, I.V.)*, into a muscle *(intramuscular, I.M.)*, into the skin *(Intradermal, I.D., intracutaneous)*, or under the skin *(subcutaneous, S.C., Sub-Q, S.Q., hypodermic, "Hypo.")* (Fig. 8–1).

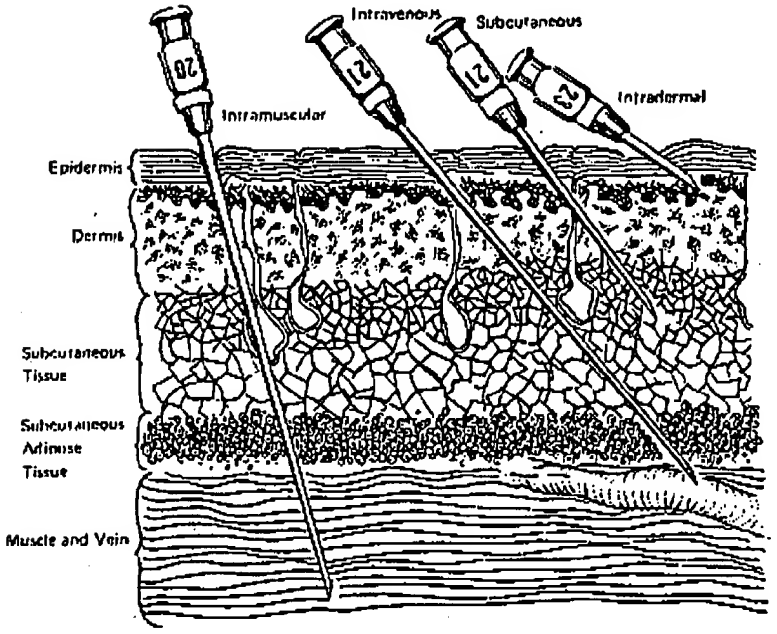


Fig. 8–1. *Routes of parenteral administration. Numbers on needles indicate size or gauge of needle based on outside diameter of needle shaft. (Turco, S. and King, R.E., Sterile Dosage Forms: Their Preparation and Clinical Applications. 3rd Ed., Courtesy of Lea & Febiger, 1987.)*

### Intravenous Route

The intravenous injection of drugs had its scientific origin in 1656 in the experiments of Sir Christopher Wren, architect of St. Paul's Cathedral and amateur physiologist. Using a bladder and quill for a syringe and needle, he injected wine, ale, opium, and other substances into the veins of dogs and studied their effects. Intravenous medication was first given to man by Johann Daniel Major of Kiel in 1662, but was abandoned for a period because of the occurrence of thrombosis and embolism in the patients so treated. The invention of the hypodermic syringe toward the middle of the 19th century created a new interest in intravenous techniques and toward the turn of the century, intravenous administration of solutions of sodium chloride and glucose became popular. Today, the intravenous administration of drugs is a routine occurrence in the hospital, although there are still recognized dangers associated with the practice. Thrombus and embolus formation may be induced by intravenous needles and catheters, and the possibility of particulate matter in parenteral solutions poses concern for those involved in the development, administration, and use of intravenous solutions.

Intravenously administered drugs provide rapid action compared to other routes of administration and because drug absorption is not a factor, optimum blood levels may be achieved with the accuracy and immediacy not possible by other routes. In emergency situations, the intravenous administration of a drug may be a life-saving procedure because of the placement of the drug directly into the circulation and the prompt action which ensues. On the negative side, once a drug is administered intravenously, it cannot be retrieved. In the case of an adverse reaction to the drug, for instance, the drug cannot be easily removed from the circulation as it could, for example, by the induction of vomiting following the oral administration of the same drug.

Although most superficial veins are suitable for venipuncture, the veins of the antecubital area (situated in front of the elbow) are usually selected for direct intravenous injection. The veins in this location are large, superficial and easy to see and enter. Most clinicians insert the needle with the bevel facing upward, at the most

acute angle possible with the vein, to ensure that the direction of flow of the injectable is that of the flow of the blood. Strict aseptic precautions must be taken at all times to avoid risk of infection. Not only are the injectable solutions sterile, the syringes and needles employed must also be sterilized and the point of entrance must be disinfected to reduce the chance of carrying bacteria from the skin into the blood via the needle. Prior to injection, administration personnel must withdraw the plunger of the syringe or squeeze a special bulb found on most I.V. sets to ensure that the needle has been properly located. In both instances, a "flashback" of blood into the administration set or the syringe indicates proper placement of the needle within the vein.

Both small and large volumes of drug solutions may be administered intravenously. The use of 1000-mL containers of solutions for intravenous infusion is commonplace in the hospital. These solutions containing such agents as nutrients, blood extenders, electrolytes, amino acids, and other therapeutic agents are generally administered through an indwelling needle or catheter by continuous drip. The drip or flow rates may be adjusted by the clinician according to the needs of the patient. Generally, flow rates of 2 to 3 mL per minute are employed. For intravenous infusion, the needle or catheter is generally placed in the prominent veins of the forearm or leg and taped firmly to the patient so that it will not slip from place during infusion. The main hazard of intravenous infusion is the possibility of thrombus formation induced by the touching of the wall of the vein by the catheter or needle. Thrombi are more likely to occur when the infusion solution is of an irritating nature to the biologic tissues. A *thrombus* is a blood clot formed within the blood vessel (or heart) due usually to a slowing of the circulation or to an alteration of the blood or vessel wall. Once such a clot circulates, it becomes an *embolus*, carried by the blood stream until it lodges in a blood vessel, obstructing it, and resulting in a blockage or occlusion referred to as an *embolism*. Such an obstruction may be a critical hazard to the patient, depending upon the site and severity of the obstruction.

Intravenously administered drugs ordinarily must be in aqueous solution; they must mix with the circulating blood and not precipitate from solution. Such an event could lead to pulmonary microcapillary occlusion and the subsequent blockage of blood passage. An intravenously delivered fat emulsion (Intralipid, 10%, Clintec) has gained acceptance for use as a source of calories and essential fatty acids for patients requiring parenteral nutrition for extended periods of time (usually for more than 5 days). The product contains up to 20% soybean oil emulsified with egg yolk phospholipids, in a vehicle of glycerin in water for injection. The emulsion is administered via a peripheral vein or by central venous infusion.

Naturally, the intravenous route is utilized in the administration of blood transfusions and it also serves as the point of exit in the removal of blood from patients for diagnostic work and for obtaining blood from donors.

In the late 1980s, automated intravenous delivery systems became commercially available for intermittent, self-administration of analgesics. Patient-controlled analgesia (PCA) has been used to control the pain associated with postoperative pain from a variety of surgical procedures, labor, sickle cell crisis, and chronic pain associated with cancer. For patients with chronic malignant pain, PCA allows a greater degree of ambulation and independence.[1]

The typical PCA device includes a syringe or chamber that contains the analgesic drug and a programmable electomechanical unit. The unit, which might be compact enough to be worn on a belt or carried in a pocket (e.g., WalkMed® PCA–Medex, Inc.), controls the delivery of drug by advancing a piston when the patient presses a button. The drug can be loaded into the device by a health care professional or dispensed from preloaded cartridges available through the manufacturer. The devices take advantage of intravenous bolus injections to produce rapid analgesia, along with slower infusion to produce steady-state opiate concentrations for sustained pain control.

The advantage of the PCA is its ability to provide constant and uniform analgesia. The typical intramuscular injection of an opiod into a depot muscular site may result in variable absorption, leading to unpredictable blood concentrations. Further, these injections are usually given when needed and are often inadequate to treat the pain. The PCA can prevent pharmacokinetic and pharmacodynamic differences between patients from interfering with the effectiveness of analgesia. Because opiod kinetics differ greatly between patients, the rates of infusion must be tailored.[2]

PCA devices can be used for intravenous, subcutaneous, or epidural administration. Gener-

the skin released. This creates a "Z" pattern that blocks infiltration of medication into the subcutaneous tissue. The injection is 2 to 3 inches deep, and a 19- to 20-gauge needle is utilized. To further prevent any staining of upper tissue, usually one needle is used to withdraw the iron dextran from its ampul, and then replaced with another for the purposes of the injection.

### Subcutaneous Route

The subcutaneous route may be utilized for the injection of small amounts of medication. The injection of a drug beneath the surface of the skin is usually made in the loose interstitial tissues of the outer surface of the upper arm, the anterior surface of the thigh, and the lower portion of the abdomen. The site of injection is usually rotated when injections are frequently given, e.g., daily insulin injections. Prior to injection, the skin at the injection site should be thoroughly cleansed. The maximum amount of medication that can be comfortably injected subcutaneously is about 1.3 mL and amounts greater than 2 mL will most likely cause painful pressure. Syringes with up to 3 mL capacities and utilizing needles with 24 to 26 gauges are used for subcutaneous injections. These needles will have cannula lengths that vary between $\frac{3}{8}$ inch to 1 inch. Most typically, subcutaneous insulin needles are between 25 to 28 gauge with needle length between $\frac{3}{8}$ to $\frac{5}{8}$ inch. Upon insertion, if blood appears in the syringe a new site should be selected.

Drugs which are irritating or those which are present in thick suspension form may produce induration, sloughing, or abscess formation and may be painful to the patient. Such preparations should be considered not suitable for subcutaneous injection.

### Intradermal Route

A number of substances may be effectively injected into the corium, the more vascular layer of the skin just beneath the epidermis. These substances include various agents for diagnostic determinations, desensitization, or immunization. The usual site for intradermal injection is the anterior surface of the forearm. A short ($\frac{3}{8}$ in.) and narrow gauge (23- to 26-gauge) needle is usually employed. The needle is inserted horizontally into the skin with the bevel facing upward. The injection is made when the bevel just disappears into the corium. Usually only about 0.1 mL volumes may be administered in this manner.

## *Official Types of Injections*

According to the USP, injections are separated into five distinct types, generally defined as follows:

1. Medicaments or solutions, or emulsions suitable for injection, bearing titles of the form, "_____ *Injection*." (Ex: Insulin Injection, USP)
2. Dry solids or liquid concentrates containing no buffers, diluents, or other added substances, and which, upon the addition of suitable solvents, yield solutions conforming in all aspects to the requirements for injections, and which are distinguished by titles of the form, "*Sterile* _____ " (Ex: Sterile Ampicillin Sodium, USP)
3. Preparations the same as those described in (2) except that they contain one or more buffers, diluents, or other added substances, and which are distinguished by titles of the form, "_____ *for Injection*" (Ex: Methicillin Sodium for Injection, USP)
4. Solids which are suspended in a suitable fluid medium and which are not to be injected intravenously or into the spinal canal, distinguished by titles of the form, "*Sterile* _____ *Suspension*." (Ex: Sterile Dexamethasone Acetate Suspension, USP).
5. Dry solids, which, upon the addition of suitable vehicles, yield preparations conforming in all respects to the requirements for Sterile Suspensions, and which are distinguished by titles of the form, "*Sterile* _____ *for Suspension*." (Ex: Sterile Ampicillin for Suspension, USP)

The form in which a given drug is prepared for parenteral use by the manufacturer depends upon the nature of the drug itself, with respect to its physical and chemical characteristics, and also upon certain therapeutic considerations. Generally, if a drug is unstable in solution, it may be prepared as a dry powder intended for reconstitution with the proper solvent at the time of its administration, or it may be prepared as a suspension of the drug particles in a vehicle in which the drug is insoluble. If the drug is unstable in the presence of water, that solvent may be replaced in part or totally by a solvent in which the drug is insoluble. If the drug is insoluble in water, an injection may be prepared as an aqueous suspension or as a solution of the drug in a suitable nonaqueous solvent, such as a vege-

table oil. If an aqueous solution is desired, a water-soluble salt form of the insoluble drug is frequently prepared to satisfy the required solubility characteristics. Aqueous or blood-miscible solutions may be injected directly into the blood stream. Blood-immiscible liquids, e.g., oleaginous injections and suspensions, can interrupt the normal flow of blood within the circulatory system, and their use is generally restricted to other than intravenous administration. The onset and duration of action of a drug may be somewhat controlled by the chemical form of the drug used, the physical state of the injection (solution or suspension), and the vehicle employed. Drugs that are very soluble in body fluids generally have the most rapid absorption and onset of action. Thus, drugs in aqueous solution have a more rapid onset of action than do drugs in oleaginous solution. Drugs in aqueous suspension are also more rapid acting than drugs in oleaginous suspension due to the greater miscibility of the aqueous preparation with the body fluids after injection and the subsequent more rapid contact of the drug particles with the body fluids. Oftentimes more prolonged drug action is desired to reduce the necessity of frequently repeated injections. These long-acting types of injections are commonly referred to as repository or "depot" types of preparations.

The solutions and suspensions of drugs intended for injection are prepared in the same general manner as was discussed previously in this text for oral solutions (Chapter 6) and oral suspensions (Chapter 7), with the following differences:

1. Solvents or vehicles used must meet special purity and other standards assuring their safety by injection.
2. The use of added substances, as buffers, stabilizers, and antimicrobial preservatives, fall under specific guidelines of use and are restricted in certain parenteral products. The use of coloring agents is strictly prohibited.
3. Parenteral products are always sterilized and meet sterility standards and must be pyrogen-free.
4. Parenteral solutions must meet compendial standards for particulate matter.
5. Parenteral products must be prepared in environmentally controlled areas, under strict sanitation standards, and by personnel specially trained and clothed to maintain the sanitation standards.
6. Parenteral products are packaged in special hermetic containers of specific and high quality. Special quality control procedures are utilized to ensure their hermetic seal and sterile condition.
7. Each container of an injection is filled to a volume in slight excess of the labeled "size" or volume to be withdrawn. This overfill permits the ease of withdrawal and administration of the labeled volumes.
8. There are restrictions over the volume of injection permitted in multiple-dose containers and also a limitation over the types of containers (single-dose or multiple-dose) which may be used for certain injections.
9. Specific labeling regulations apply to injections.
10. Sterile powders intended for solution or suspension immediately prior to injection are frequently packaged as *lyophilized* or freeze-dried powders to permit ease of solution or suspension upon the addition of the solvent or vehicle.

## Solvents and Vehicles for Injections

The most frequently used solvent in the large-scale manufacturer of injections is *Water for Injection, USP*. This water is purified by distillation or by reverse osmosis and meets the same standards for the presence of total solids as does *Purified Water, USP*, not more than 1 mg per 100 mL. Water for Injection, USP and may not contain added substances. Although water for injection is not required to be sterile, it must be pyrogen-free. The water is intended to be used in the manufacture of injectable products which are to be sterilized after their preparation. Water for injection should be stored in tight containers at temperatures below or above the range in which microbial growth occurs. Water for injection is intended to be used within 24 hours following its collection. Naturally, the water should be collected in sterile and pyrogen-free containers. The containers are usually glass or glass-lined.

*Sterile Water for Injection, USP* is water for injection which has been sterilized and packaged in single-dose containers of not greater than 1-liter size. As water for injection, it must be pyrogen-free and may not contain an antimicrobial agent or other added substance. This water may contain a slightly greater amount of total solids than water for injection due to the leaching of solids from the glass-lined tanks during the steriliza-

tion process. This water is intended to be used as a solvent, vehicle or diluent for already-sterilized and packaged injectable medications. The one-liter bottles cannot be administered intravenously because they have no tonicity. Thus, they are used for reconstitution of multiple antibiotics. In use, the water is aseptically added to the vial of medication to prepare the desired injection. For instance, a suitable injection may be prepared from the dry powder, Sterile Ampicillin Sodium, USP, by the aseptic addition of sterile water for injection.

*Bacteriostatic Water for Injection, USP* is sterile water for injection containing one or more suitable antimicrobial agents. It is packaged in prefilled syringes or in vials containing not more than 30 mL of the water. The container label must state the name and proportion of the antimicrobial agent(s) present. The water is employed as a sterile vehicle in the preparation of small volumes of injectable preparations. The presence of the bacteriostatic agent gives the flexibility for multiple-dose vials. If the first person to withdraw medication inadvertently contaminates the vial contents, the preservative will destroy the microorganism. Because of the presence of antimicrobial agents the water must only be used in parenterals that are administered in small volumes. Its use in parenterals administered in large volume is restricted due to the excessive and perhaps toxic amounts of the antimicrobial agents which would be injected along with the medication. Generally, if volumes of greater than 5 mL of solvent are required, sterile water for injection rather than bacteriostatic water for injection is preferred. In using bacteriostatic water for injection, due regard must also be given to the chemical compatibility of the bacteriostatic agent(s) present with the particular medicinal agent being dissolved or suspended.

*Sodium Chloride Injection, USP* is a sterile isotonic solution of sodium chloride in Water for Injection. It contains no antimicrobial agents. The sodium and chloride ion contents of the injection are approximately 154 mEq of each per liter. The solution may be used as a sterile vehicle in preparing solutions or suspensions of drugs for parenteral administration.

*Bacteriostatic Sodium Chloride Injection, USP* is a sterile isotonic solution of sodium chloride in Water for Injection. It contains one or more suitable antimicrobial agents which must be specified on the labeling. Sodium chloride is present at 0.9% concentration to render the solution isotonic. For the reasons noted previously for bacteriostatic water for injection, this solution may not be packaged in containers greater than 30 mL in size. When this solution is used as a vehicle, care must be exercised to assure the compatibility of the added medicinal agent with the preservative(s) present as well as with the sodium chloride. Further, USP labeling requirements demand that the label state, "Not for Use in Newborns." This new labeling statement was the result of problems encountered with neonates and the toxicity of the bacteriostat, i.e., benzyl alcohol. This toxicity may result from the high cumulative amounts (mg/kg) of benzyl alcohol and the limited detoxification capacity of the neonate liver. This solution has not been reported to cause problems in older infants, children, or adults.

*Ringer's Injection, USP* is a sterile solution of sodium chloride, potassium chloride, and calcium chloride in water for injection. The three agents are present in concentrations similar to that found in physiologic fluids. The solution is employed as a vehicle for other drugs, or alone as an electrolyte replenisher and fluid extender. *Lactated Ringer's Injection, USP* has different quantities of the same three salts in Ringer's Injection and contains sodium lactate. This injection is a fluid and electrolyte replenisher and a systemic alkalizer.

### Nonaqueous Vehicles

Although an aqueous vehicle is generally preferred for an injection, its use may be precluded in a formulation due to the limited water solubility of a medicinal substance or its susceptibility to hydrolysis. When such physical or chemical factors limit the use of a wholly aqueous vehicle, the pharmaceutical formulator must turn to one or more nonaqueous vehicles.

The selected vehicle must be nonirritating, nontoxic in the amounts administered, and nonsensitizing. Like water, it must not exert a pharmacologic activity of its own, nor may it adversely affect the activity of the medicinal agent. In addition, the physical and chemical properties of the solvent or vehicle must be considered, evaluated, and determined to be suitable for the task at hand before it may be employed. Among the many considerations are the solvent's physical and chemical stability at various pH levels, its viscosity, which must be such as to allow ease of injection (syringeability), its fluidity, which must be maintained over a fairly wide tempera-

ture range, its boiling point, which should be sufficiently high to permit heat sterilization, its miscibility with body fluids, its low vapor pressure to avoid problems during heat sterilization, and its constant purity or ease of purification and standardization. There is no single solvent that is free of limitations, and thus the cross-consideration and the assessment of each solvent's advantages and disadvantages help the formulator determine the most appropriate solvent for use in a given preparation. Among the nonaqueous solvents presently employed in parenteral products are fixed vegetable oils, glycerin, polyethylene glycols, propylene glycol, alcohol, and a number of lesser used agents as ethyl oleate, isopropyl myristate, and dimethylacetamide. These and other nonaqueous vehicles may be used provided they are safe in the amounts administered and do not interfere with the therapeutic efficacy of the preparation or with its response to prescribed assays and tests.

The USP specifies restrictions on the fixed vegetable oils which may be employed in parenteral products. For one thing, they must remain clear when cooled to 10°C to ensure the stability and clarity of the injectable product upon storage under refrigeration. The oils must not contain mineral oil or paraffin, as these materials are not absorbed by body tissues. The fluidity of a vegetable oil generally depends upon the proportion of unsaturated fatty acids, such as oleic acid, to saturated acids, such as stearic acid. Oils to be employed in injections must meet officially stated requirements of iodine number and saponification number.

Although the toxicities of vegetable oils are generally considered to be relatively low, some patients exhibit allergic reactions to specific oils. Thus, when vegetable oils are employed in parenteral products, the label must state the specific oil present. The most commonly used fixed oils in injections are corn oil, cottonseed oil, peanut oil, and sesame oil. Castor oil and olive oil have been used on occasion.

By the selective employment of solvent or vehicle, a pharmacist can prepare injectable preparations as solutions or suspensions of a medicinal substance in either an aqueous or nonaqueous vehicle. For the most part, oleaginous injections are administered intramuscularly. They must not be administered intravenously as the oil globules will occlude the pulmonary microcirculation. Some examples of official injections employing oil as the vehicle are presented in Table 8–1.

## *Added Substances*

The USP permits the addition of suitable substances to the official preparations intended for injection for the purpose of increasing their stability or usefulness, provided the substances are not interdicted in the individual monographs and are harmless in the amounts administered and do not interfere with the therapeutic efficacy of the preparation or with specified assays and tests. Many of these added substances are antibacterial preservatives, buffers, solubilizers, antioxidants, and other pharmaceutical adjuncts. Agents employed solely for their coloring effect are strictly prohibited in parenteral products.

The USP requires that one or more suitable substances be added to parenteral products that are packaged in multiple-dose containers, to prevent the growth of microorganisms regardless of the method of sterilization employed, unless

**Table 8–1. Examples of Some Injections in Oil**

| *Injection* | *Oil* | *Category* |
|---|---|---|
| Dimercaprol Injection | Peanut | Antidote to arsenic, gold and mercury poisoning |
| Estradiol Cypionate Injection | Cottonseed | Estrogen |
| Estradiol Valerate Injection | Sesame or Castor | Estrogen |
| Fluphenazine Decanoate Injection | Sesame | Antipsychotic |
| Fluphenazine Enanthate Injection | Sesame | Antipsychotic |
| Hydroxyprogesterone Caproate Injection | Sesame or Castor | Progestin |
| Progesterone in Oil Injection | Sesame | Progestin |
| Testosterone Cypionate Injection | Cottonseed | Androgen |
| Testosterone Cypionate plus Estradiol Cypionate Injection | Cottonseed | Androgen plus Estrogen |
| Testosterone Enanthate Injection | Sesame | Androgen |

otherwise directed in the individual monograph or unless the injection's active ingredients are themselves bacteriostatic. Such substances are used in concentrations that prevent the growth of or kill microorganisms in the preparations. Because many of the usual preservative agents are toxic when given in excessive amounts or irritating when parenterally administered, special care must be exercised in the selection of the appropriate preservative agents. For the following preservatives, the indicated maximum limits prevail for use in a parenteral product unless otherwise directed: for agents containing mercury and the cationic, surface-active compounds, 0.01%; for agents like chlorobutanol, cresol, and phenol, 0.5%; for sulfur dioxide as an antioxidant, or for an equivalent amount of the sulfite, bisulfite, or metabisulfite of potassium or sodium, 0.2%.

In addition to the stabilizing effect of the additives, the air within an injectable product is frequently replaced with an inert gas, such as nitrogen, to enhance the stability of the product by preventing chemical reaction between the oxygen in the air and the drug.

## *Methods of Sterilization*

The term *sterilization*, as applied to pharmaceutical preparations, means the complete destruction of all living organisms and their spores or their complete removal from the preparation. Five general methods are used for the sterilization of pharmaceutical products:

1. Steam sterilization
2. Dry-heat sterilization
3. Sterilization by filtration
4. Gas sterilization
5. Sterilization by ionizing radiation

The method used in attaining sterility in a pharmaceutical preparation is determined largely by the nature of the preparation and its ingredients. However, regardless of the method used, the resulting product must pass a test for sterility as proof of the effectiveness of the method and the performance of the equipment and the personnel.

### Steam Sterilization

Steam sterilization is conducted in an autoclave and employs steam under pressure. It is recognized as the method of choice in most cases where the product is capable of withstanding such treatment (Fig. 8–3).

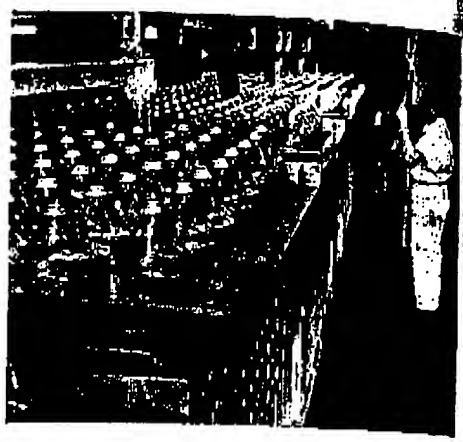

Fig. 8–3. *Autoclaving of intravenous electrolyte solutions. (Courtesy of Abbott Laboratories.)*

Most pharmaceutical products are adversely affected by heat and cannot be heated safely to the temperature required for dry-heat sterilization (about 170°C). When moisture is present, bacteria are coagulated and destroyed at a considerably lower temperature than when a moisture is absent. In fact, bacterial cells with a large percentage of water are generally killed rather easily. Spores, which contain a relatively low percentage of water, are comparatively difficult to destroy. The mechanism of microbial destruction in moist heat is thought to be by denaturation and coagulation of some of the organism's essential protein. It is the presence of the hot moisture within the microbial cell that permits destruction at relatively low temperature. Death by dry heat is thought to be by the dehydration of the microbial cell followed by a slow burning or oxidative process. Because it is not possible to raise the temperature of steam above 100°C under atmospheric conditions, pressure is employed to achieve higher temperatures. It should be recognized that the temperature, not the pressure, is destructive to the microorganisms and that the application of pressure is solely for the purpose of increasing the temperature of the system. Time is another important factor in the destruction of microorganisms by heat. Most modern autoclaves have gauges to indicate to the operator the internal conditions of temperature and pressure and a timing device to permit the desired exposure time for the load. The usual